4

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/601,138	10/26/2000	Jens Fogh	FOGH1	5676

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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/601,138	FOGH ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-19,23,24,26-31,36-46 and 48* is/are pending in the application.

4a) Of the above claim(s) *38-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-19,23-31 and 48* is/are rejected.

7)☒ Claim(s) *36 and 37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The examiner is acknowledging the Amendment under Rule 1.115, filed March 26, 2004. Claims 2, 3, 20-22, 25, 32-5, 47 and 49-51 have been cancelled. 1, 4-19, 23, 24, 26-29, 36-40, 45 46, 48 have been amended. Claims 38-46 are withdrawn from consideration by examiner as directed to the non-elected invention; see 37 CFR 1.142(b). Claims 1, 4-19, 23, 24, 26-31, 36-37, 38-46 and 48 are pending. Claims 1, 4-19, 23, 24, 26-31, 36-37 and 48 in part related to acute intermittent porphyria (AIP) and the respective enzyme, porphobilinogen deaminase (PBGD), are the subject of this Office Action.

Detailed Office Action

1. Objections

Claim 1 is objected to because the name of the enzyme in line 14 should be spelled porphobilinogen deaminase. Furthermore the adjective "human" in the third line is abundant, because a human being as in hi/her body only human enzymes, absent teaching to he contrary.

Please delete "a" before the word "recombinantly" in claim 5.

The word "sterile" in claim 9 should be replaced with "sterilely". Furthermore, as we do not treat patients with anything which is not sterile, the examiner proposes to cancel the claim, because it limits claim 1 only semantically.

Claim 48 is objected to under 37 CFR 1.75 as being an exact duplicate of claim 4.

2. Rejections

2. 1. 35 U.S.C. 112, second paragraph

Rejection of claims 2, 3, 20, 21, 22, 25, 47 and 51 made in the Office Action of Sept. 26 2003 (previous Office Action) is moot because the claims have been cancelled.

Rejection of 24 for the use of the tem "substantially all" is withdrawn because Applicants arguments are found persuasive.

Rejection of claims 36 and 37 made in the previous Office Action is withdrawn, because the claims have been amended.

3.2. 35 U.S.C. 112, first paragraph

3.2.1. Lack of written description

Claims 1-19, 21-32, 35 and 47-51 were rejected in the previous Office Action under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Rejection of claims 2-3, 21-22, 32, 35, 47 and 49-51 is moot because the claims have been canceled.

Rejection of claim 48 specifically because neither the claims nor the specification disclose any enzymatically active fragment of PBGD or analogs thereof is withdrawn because the claim has been amended.

Rejection of claim 1, 4-19, 23-31 and 48 is still not withdrawn, because although the claim has been amended, the claim does not recite the structure, i.e., does not identify the product to be used in the claimed method. In the current form the claim as read on the elected species of AIP and PBGD is as follows:

1. A method for treatment or prophylaxis of disease caused by deficiency, in a human subject, a human enzyme belonging to the heme biosynthetic pathway, the method comprising administering, to the subject, and effective amount of said enzyme wherein the disease is AIP and the enzyme is PBGD.

Claim 1 is generic because it is directed to use of any known and to be identified PBGP. Applicant provides only two species of the claimed genus of enzymes, the human PBGD encoded by SEQ ID NO: 1 and 12. Applicants do not describe the use of other species (forms) of human PBGD. Thus, the scope of the claims covers the use of the enzymes not disclosed by Applicants. Having at hands two representative species of the claimed genus is not sufficient for providing identifying characteristics of any species of the claimed genus, including proteins that have required enzymatic activity and are mutants of human PBGP or their fragments.

In summary, because claim(s) contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, the claims are rejected.

Response to Applicants' arguments

In their REMARKS, on page 12, line 3 Applicants write,

"While the Examiner says that they are 'representative' [two species encoded by SEQ ID NO: 1

> and 12], it is clear that the Examiner means to say that they are not representative.
>
> However, this blithely ignores the disclosure of seven more enzymes and eight more diseases."

Applicants' arguments have been fully considered but are found not persuasive for the following reasons. The species encoded by DNA molecules set forth by SEQ ID NO: 1 and 12 are representatives of the genus of all PBGD enzymes, however, they are not species that identify the structure of the whole genus as broadly used in the claim. Is the Applicants intention to use, for example, enzymatically active mutants of PBGD taught by Brownlie P. D. et al. (The three-dimensional structure of mutants of porphobilinogen deaminases: Toward an understanding of the structural basis of acute intermittent porphyria, Protein Science, 1994, 3, 1644-1650; included in Information Disclosure Statement)? It seems that in 1994 there were at least 52 known mutants of which about 18 were inactive; see Table I in the article. Applicants themselves teach that there are about 100 allelic variants of human PBGD.

As to the blithely ignoring the disclosure of seven more enzymes and eight more diseases, it is irrelevant whether these enzymes and diseases are disclosed or not, because the enzymes whose deficiency is related to illnesses other than acute intermittent porphyria, cannot be used for treatment of the very illness that is acute intermittent porphyria. The enzymes are not interchangeable when it comes to the treating eight illnesses. Furthermore, Applicants' attention is directed to the fact that at

this stage of prosecution the examined invention is the elected species, the method of treating or preventing AIP by administering to a patient a product that is PBGD.

3.2.2. Scope of enablement

Claims 1-20, 22-31, 32, 35, and 47-51 were rejected in the previous Office Action for scope of enablement. Rejection of claims 2-3, 20-22, 32, 35, 47 and 49-51 is moot because the claims have been canceled.

Rejection of claim 48 specifically because neither the claims nor the specification disclose any enzymatically active fragment of PBGD or analogs thereof is withdrawn because the claim has been amended.

Rejection of claim 1, 4-19, 23-31 and 48 is withdrawn, because the claims have been amended.

3.3. 35 USC, section 103

Claims 1-19, 22-31, 32, 35 and 47-51 were rejected under 35 U.S.C, 103(a) in the previous Office Action. Rejection of claims 2-3, 20-22, 32, 35, 47 and 49-51 is moot because the claims have been canceled.

Claims 1, 4-19, 23-31 and 48 are rejected as being unpatentable over Raich et al. "Molecular cloning and complete primary sequence of human erythrocyte porphobilinogen deaminase " (*Nucleic Acid Research*, 1986, 14, 5955-5698) and further in view of many publications on enzyme replacement therapy, for example Beutler E. et

al, "Enzyme replacement therapy for Gaucher Disease" (*Blood*, 1991, 78, 1183-1189). The reasons were explained in the previous Office Action.

Traversing the rejection Applicants write,

> "We argue that this prima facie case was rebutted by the showing of a longfelt need for a therapy for AIP, coupled with a long-term failure of others to apply replacement therapy for AIP. We showed that replacement therapy has been known since 1966, that the connection between PBGD and AIP has been known since 1972, and that the PBGD gene has been known since 1986.(Our priority application was filed in 1998, twelve years later)",

REMARKS, page 15, the last paragraph .

Applicants' arguments have been fully considered but are found not persuasive for the following reasons. First of all, the long felt need for a therapy for AIP was provided by using drugs instead of the PBGD. Secondly, Applicants are silent as to any failures of others to apply enzyme replacement therapy for AIP. One skilled in the art realizes that although the enzyme therapy is the most rational approach to cure conditions related to its deficiency, this does not it mean that the approach is used immediately after discovering the gene a mutation of which is responsible for the condition. Applicants failed to provide an evidence why all active forms of PBGD known before the instant application was filed failed to provide any curative effect, whereas the same forms of enzyme broadly included in the claimed method work

properly starting 1998 when Applicants filed the provisional application. In summary, this prima facie case has not been rebutted.

In conclusion, in the current state of art, the enzyme replacement therapy for AIP using PBGD may be non-obvious only when the enzyme to be used is novel i.e., has a novel structure.

4. Conclusion

Claims 1, 4-19, 23-31 and 48 are rejected. Claim 36 and 37 are objected to as dependent on rejected claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The reasons for allowable subject matter are explained in the previous Office Action.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1652

Patent Examiner